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in the Prophylaxis of Tyhoid Fever

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MEMORANDA CONCERNING VACCINATION IN THE PROPHYLAXIS OF TYPHOID FEVER

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The idea of preventing the development of disease by creating a hypernormal resistance in the human organism is one of the first conceptions of Pasteur, after his discovery of microbes, and it is not to be forgotten that the first preventive method for securing such protection from disease in man was developed by Pasteur and has come to us practically unchanged to-day as the preventive treatment of rabies. In this particular disease it is to be recalled that the hyper-resistant state of the patient is obtained by a rapidly intensive process of vaccinating the patient by successive hypodermic injections of material containing the living organisms of the disease itself, but by initial doses of such organisms of so diminished virulence that the induced resistance of the patient permits the rapid increasing of virulent doses of these organisms to the point of development of human resistance in the patient, so great as to render impossible the development of the disease of rabies, even when he had been inoculated with very virulent material previous to his vaccination process.

Following this brilliant achievement of Pasteur, methods of vaccination established upon these fundamental principles of inoculating more or less avirulent germs of the disease in progressive intensification of virulence have been extensively experimented with in the laboratory and to some extent applied in treatment of disease.

The first experiments of vaccination with living organisms, logically led rapidly to the trial of methods of vaccination by the use of bacterial extracts, or dead bacteria, instead of the living germs of diminished virulence.

Methods of vaccination in which sterilized cultures of various microbes could be utilized date back for many years and such methods will be found among the early works of Pfeiffer. The first use of sterilized cultures of virulent germs for a vaccination method of treating disease in man was made by Haffkine, and this use of sterile cultures of the bacillus of cholera was the basis of Haffkine's method of prophylaxis for the prevention of cholera, which he so extensively practised in India and has so completely established.

With the success of Haffkine's method in cholera, so distinctly an intestinal infectious disease, our most logical deduction would invite experiment of the similar method for the vaccination treatment of typhoid fever, which is itself so distinctly an intestinal infection; and experiments with such vaccine were made many years ago. The principal experimenter in this work is Almroth Wright, to whose persistence and long continued advocacy as a method of typhoid prophylaxis the principal credit for the status of this vaccine treatment is due.

The first considerable utilization of this vaccine was made under Wright's direction, inoculating English troops in India that were particularly exposed to typhoid, inoculating troops in typhoid infected barracks at home or abroad, and in inoculation of troops embarked for service in the Boer War.

The results obtained by these preventive measures were considered quite satisfactory and this method was extensively controlled and utilized in other countries.

There are three proposed methods of preparing this vaccine matter, but the method of utilizing the vaccine is practically the same.

Of the three methods of preparing vaccine now, in the foreground is the German method, which consists in growing a medi-

um virulent strain of *bacillus typhosus,* inoculated upon a broad surface of the usual agar media, the culture then incubated for forty-eight hours, the resultant growth of bacteria being then washed off with sterile physiological salt solution, in which solution the number of typhoid bacilli per c.c. is then determined by the method subsequently to be described, and this solution then diluted with the same physiological salt solution to make a solution of standardized bacteria per c.c. Two strengths of solution are made: (A) in which the solution contains 500,000,000 typhoid bacilli per c.c.; and (B), solution which contains 1,000,000,000 typhoid bacilli per c.c.

The German method of producing the typhoid vaccine is that followed in the laboratory of the United States Army Service.

The English method of producing the typhoid vaccine is somewhat different, as it was devised by Wright and slightly perfected by Leishman. The method consists in inoculating a carefully prepared buillon of standardized alkalinity of 10 (Eyre scale) with a usual not particularly virulent strain of typhoid bacillus. The cultures are then grown in flasks, affording as large surface as possible, in the incubator at blood temperature, from twenty-four to forty-eight hours, preferably the latter. When grown under such conditions, the usual strain will produce at the end of forty-eight hours a culture of which each c.c. will contain something over 1,000,000,000 typhoid bacilli, perhaps 1,500,000,000. The actual number of bacilli contained in these growths is then determined by the process devised in Wright's laboratory and carried out very simply as follows:

It is recalled that the number of red blood corpuscles in human blood is well known and varies slightly. If, therefore, an equal volume of such blood be mixed with equal volume of culture or emulsion of typhoid bacilli, the resultant mixture may be smeared upon a slide, stained with any good blood stain, and the relative number of bacilli to that of red blood corpuscles is then easily determined by a small microscopic examination, counting the bacilli and red corpuscles in one or more fields observed.

Having determined this proportionate count, the actual number of bacilli per c.c. in the culture examined, results from a simple calculation. The culture or emulsion of typhoid bacilli to be standardized, is then properly diluted according to the determined count to bring the actual number in the diluted blood to any desired standard. This method is utilized at present for all standardization of typhoid bacilli cultures or emulsions used as vaccines.

Referring then to the English method of typhoid vaccine production, the cultures previously obtained are standardized by the methods just described to two dilutions: A—containing 500,000,000 typhoid bacilli per c.c., and B solution—containing 1,000,000,000 of these germs per c.c.

The third prominently proposed vaccine varies substantially from either the German or English vaccines just described. The third vaccine is advocated most strongly by Vincent and contains elements which may prove to make it superior to the other two, but Vincent's vaccine has not had anything like the broad, extensive application in actual prophylactic work.

Vincent's method involves the culture of many selected strains of typhoid bacilli in his effort to produce a polyvalent vaccine. The selected strains are inoculated all together upon the usual agar and grown in the incubator for forty-eight hours, exactly as in the case of the German method. The resultant growth is carefully washed off with physiological solution, as in the German method, but this resultant emulsion of typhoid bacilli is then incubated at blood temperature to secure an effective maceration and the effusion of the endobacillary substances into the fluid. The macerated fluid is then centrifugalized and the resultant super-natant, clear liquid is removed from all sediment and shaken up with ether. The ether is utilized here as an ultimate sterilizer, as Vincent avoids any application of heat to his vaccine beyond that of blood temperature.

After agitation with ether, the heating of this fluid to blood temperature brings about the rapid ether removal by evaporation and the clear liquid remaining constitutes the third vaccine, which is that advocated by Vincent.

Of this third vaccine, two strengths are

utilized: Solution A—in which the emulsion of polyvalent typhoid bacilli has been carried in the incubator for twenty-four hours only, and solution B—in which the same emulsion was carried in the incubator for forty-eight hours.

For producing a typhoid immunity with Vincent four injections are given to each patient every eight to ten days, the first injection being one-fourth of a c.c. of the twenty-four hours' incubated emulsion, and the second dose three-fourths of a c.c. of the same emulsion. The third dose contains one c.c. of the forty-eight hour incubated emulsion and the fourth dose contains two c.c. of this latter emulsion.

It is claimed for Vincent's method of provoking immunity that a better grade of intensely organic resistance is obtained with less, practically no, discomfort of the patients treated.

Returning now to the German and English vaccines, their method of use is the same and the process of vaccination consists in the administration of three injections to each person in whom it is desired to provoke a typhoid immunity. The vaccines prepared in Germany, England or this country are standardized as previously described and to these solutions a dose of lysol, or trikresol, to the amount of about one-fourth of one per cent. is utilized for the preservation of the sterility of this vaccine matter after that sterility of the standardized solutions of the typhoid bacilli has once been produced at the laboratory.

After producing the vaccine solutions, diluting them to obtain the proper standard desired, these solutions are heated carefully in a water bath to about 53 degrees centigrade (Leishman), or 55 to 57 degrees centigrde (German and American Laboratory Uses).

It is preferable not to allow the heat of these vaccine solutions to go higher than 53 degrees and it is found that the heating of these solutions of living typhoid bacilli for one, to one and one-half hours, at 53 degrees centigrade produces their complete sterilization. It has been pointed out that without such heating the mere addition of the small quantities of antiseptic previously noted would produce the sterilization of that fluid after a few days time, but the experimental work of Leishman would indicate that the heating to 53 degrces centigrade in no way lessens the immunity production power of the vaccinc and is, therefore, retained as an additional safeguard for sterility.

After sterilization and then the addition of antiseptic the vaccine of standards A and B are carefully scaled in glass ampullae, in which packages, protected from the light and kept relatively cool, it has been found that the power of immunity production, and therefore, practical utility of the vaccine is retained for at least three months.

The production of immunity with these vaccines is obtained by three injections to the patient. The first injection should be a dose of 500,000,000 typhoid bacilli, followed ten days later by a second injection of 1,000,000,000 typhoid bacilli, and this followed eight to ten days later by a further dose of 1,000,000,000 typhoid bacilli.

The English authority is inclined to consider the first two injections sufficient to provoke a satisfactory immunity, at the same time considering that three or even four injections would be of advantage to the degree of immunity resulting.

The use of vaccine in troops involves, as far as possible, the injection of three doses.

It is to be recalled that this method of protection from typhoid fever by such vaccines dates back already fifteen years. The results of the extensive vaccination in the English army since that period have come from more and more extensive utilization of such vaccination; and results of this method of vaccination in Germany are available from the colonial troops for the last seven years; and results for more than two years' utilization in the United States are also available.

Speaking in general terms, it can be said that this vaccine method is without danger; that carried out as at present, it involves very slight inconvenience for any of the persons so inoculated and practically in no case does it result in any symptoms of severity. The reports of the use of this vaccine with the troops actually in active duty, show conclusively that the large vaccine treatment does not interfere to any extent with any of the men on active duty.

It is quite demonstrative of the freedom of this treatment from undesirable symptoms that in many cases of vaccination of troops where the matter has been left entirely to the voluntary action of the soldier, these soldiers have not failed to continue the treatment right through the three injections without complaint. There can be no doubt of the very great immunity resulting from this treatment.

The statistics of troops in campaign and in infected localities, where experiments have been made on a large scale, where vaccinations have been made on troops working together with troops not vaccinated; the result of these experiments show most conclusively the immunizing value of this vaccine treatment.

As a matter of debate, there exists, however, the question of duration of such acquired immunity. The work of more recent years has shown unfortunately that there existed grave defects in much of the vaccine utilized in the first years of this method of anti-typhoid vaccination. These defects have been corrected in the work of more recent years, but knowledge of the previous defective vaccines quite invalidates any clear determination of the duration of resultant immunity.

There is good authority — German, French and English—to believe that in most cases an immunity would be gained that would last possibly two years. There is some statement that reported cases would indicate a possibility that the acquired immunity, sometimes lasted only a few months. As a result, however, of most exhaustive investigation, the official governmental report in France, recently made, advocates the use of this vaccine for all troops called into service; for all troops in service in notably infected localities and for all persons whose career brings them to any special exposure of the typhoid infection (nurses in hospital wards containing typhoid cases, physicians and all others actually engaged in caring for patients in time of typhoid epidemic, etc.).

The question of anti-typhoid vaccination in this country has been brought most actively to the front by reason of the particular interest and activity of the laboratories of the United States Army Service, and these activities are quite exhaustively described in the report of the surgeon general of 1911.

It is interesting to note that throughout the year 1910, 16,000 persons were subjected to this vaccine treatment, whereas in the first six months of 1911, about 28,000 were thus immunized. Throughout these treatments the amount of severe general reaction resulting from these vaccine injections are noted after the first injection one-tenth of one per cent., the same after second injection, and eight one-hundredths of one per cent. for the third injection. That is to say, ninety-nine per cent. of the people treated show no particularly marked reaction.

From these army laboratories, also, vaccine for the immunizing of 2,752 men of the navy has been supplied and for those other than members of the military service of the United States, the following amounts of vaccine were distributed from the army laboratories in 1910:

Vaccine Used in 1910.

	C.c.
Department of Health of Buffalo, N. Y.	708
Florida State Board of Health	786
Iowa State Board of Health	144
Texas State Board of Health	36
Georgetown University, D.C.	12
North Carolina Medical College	244
Tufts Medical School	12
Neurological Laboratory	60
National Guard of Missouri	18
National Guard of New Mexico	1,242
National Guard of Virginia	123
Marine Hospital Service	207
United States Navy	3,281
Doctors, for private use	378
Total outside of Army for 1910	7,251
Total used in Army for 1910	68,592
Grand total	75,843

For the first six months of 1911, 112,772 cubic centimetres of vaccine matter have been used in the army service, and 23,238 cubic centimeters of these vaccines have been distributed for use other than by members of the army. Details of the distribution outside of the army for the first six months of 1911, follow:

	C.c.
Iowa University College of Medicine	36
Austin Sanitarium	132
Hon. Chas. L. Bartlett, M.C.	3
Louisiana National Guard	120
Maryland National Guard	1,500
Massachusetts National Guard	348
Minnesota National Guard	156
Mississippi National Guard	172
Missouri National Guard	2,472
New York National Guard	4,800
North Carolina National Guard	300
Ohio National Guard	769
South Carolina National Guard	1,204
Virginia National Guard	1,482
Wisconsin National Guard	12
Public Health and Marine Hospital Service	36
Virginia Military Institute	18
Doctors, for private use	2,122
United States Navy	7,556
Total outside of Army	23,238
Total used in Army	112,772
Grand total	136,010

The widely advertised utilization and results of anti-typhoid vaccination in the troops in Texas last year has produced a quite general movement towards the utilization of this method. A considerable effort has been made by some of the members of the medical profession throughout the country to obtain a more general vaccine immunity as a general protection against typhoid, and considerable activity has been shown in the national guard throughout the States to secure the immunization of the militia troops.

Up to this date in the State of New York from 5,000 to 6,000 doses of vaccine have been utilized in the troops of the national guard, the actual number of men enlisted in the State being 15,000. The vaccine thus far used for immunizing those who wish to submit themselves to this treatment has been secured from the laboratories, of the Army of the United States. It is supplied on requisition from the adjutant General's office of this State and the amount supplied is charged to the respective fund of the National Guard at the rate of twelve and one-half cents per dose. The method of proceeding to such vaccination in the troops of the National Guard of this State is that those military surgeons thus serving, that are willing to devote their services, offer to perform a vaccination and receive on requisition the proper vaccine.

The offer to vaccinate any number of the National Guard is made by such surgeon undertaking the service, who then vaccinates such members of the troop as are willing to accept such vaccination.

From reports of similar activity in other States, it would seem that it would not be difficult to secure volunteers to a considerable portion of the enlisted service, if the activity of the medical officers, as well as the military command should be actively directed to this end.

It is a requirement of the military service of the United States Army that each enlisted man shall be thus immunized. It has been for some years required in the German army that every soldier in the colonial troops shall be thus immunized and in many foreign armies, France and Italy for example, considerable bodies of troops are thus protected by vaccination, which is urged whenever such troops are detailed for duty in a possibly infected locality .